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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61F 2/06, 6/06, A61K 37/38, 9/50, 9/14, C07K 15/06, 17/02, 17/14

A1

(11) International Publication Number: WO 94/26208

(43) International Publication Date: 24 November 1994 (24.11.94)

(21) International Application Number: PCT/US94/05262

(22) International Filing Date: 12 May 1994 (12.05.94)

(30) Priority Data:
08/062,886 17 May 1993 (17.05.93) US

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(81) Designated States: CA, FI, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHODS AND FORMULATIONS FOR USE IN TREATING OOPHORECTOMIZED WOMEN

(57) Abstract

Compositions and methods which are effective to prevent symptoms of loss of ovarian function (e.g., in oophorectomized women) over a period of time are described, consisting essentially of an effective amount of an estrogenic composition and an effective amount of an androgenic composition. The levels of estrogens and androgens employed are sufficient to reduce bone mineral density loss and minimize other side effects observed after oophorectomy, and at such low doses as to minimize any adverse impact on the patient's long-term prognosis or (in the case of testosterone) result in additional side effects.

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METHODS AND FORMULATIONS FOR USE IN TREATING OOPHORECTOMIZED WOMEN

Background of the Invention

This invention relates to methods for treating oophorectomized women or women with other forms of ovarian failure, as well as to formulations for use in such methods. More particularly, the present invention is directed to methods and preparations effective for extended periods of time in preventing adverse symptoms associated with the loss of ovarian function in oophorectomized women or women with other forms of ovarian failure.

Oophorectomy and salpingo-oophorectomy are frequently performed in the United States, alone or with a hysterectomy. The most common indication is the treatment of uterine fibroids; other indications include malignancy and other benign gynecological disorders. In 1984, there were 498,000 such procedures performed in the U.S. As a consequence of oophorectomy, there is a marked reduction in serum estradiol and serum testosterone levels. Common side effects reported to occur as a result of these reductions in serum hormone levels after oophorectomy include: hot flashes, vaginal dryness and bone loss. Additional side effects that have been reported in some patients include: sweating, headache, depression, lability in mood, nausea and/or vomiting, nervousness, insomnia, pollakisuria, weight gain, sleepiness, dizziness, decreased libido and mild breast tenderness or swelling.

Current standard treatment of oophorectomized women calls for administration of an estrogen, or an estrogen and an androgen. Typical treatment protocols have involved the administration of: an oral estrogen alone (such as conjugated estrogens or esterified estrogens) or with an oral androgen (such as methyltestosterone); transdermal estrogen (such as estradiol); and injectable pellets of estrogen alone, or with testosterone [Stanczyk, F.Z. et al., "A randomized comparison of nonoral estradiol delivery in postmenopausal women," Am. J. Obstet. Gynecol. 159: 1540-6 (1988); Chetkowski, R.J. et al., "Biologic effects of transdermal estradiol," N. Engl. J. Med. 314: 1615-20 (1986); Ralston, S.H. et al., "Effect of

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any loss of bone mineral density (BMD) [Genant, H. et al., "Quantitative computed tomography of vertebral spongiosa: a sensitive method for detecting early bone loss after oophorectomy," Ann. Intern. Med. 97: 699-705 (1982)]. Recent clinical studies on women with a medical oophorectomy (induced by a gonadotropin releasing hormone agonist, GnRHA) have clearly shown that this is incorrect, and that a conventional oral dose of 0.625 to 0.9 mg of conjugated estrogens is inadequate. While higher doses of estrogens may be employed to prevent loss of BMD, exogenous estrogen is associated with a significant increase in the risk of breast cancer. This is a dose-dependent effect, so that the lowest possible dose of estrogen to prevent adverse symptoms is desirable.

Preliminary results with the addition of a small dose of oral replacement androgen (1.25 to 2.5 mg of methyltestosterone) to the GnRHA plus conjugated estrogens regimen show protection against the loss of BMD. Unfortunately, the addition of the methyltestosterone has produced detrimental changes in serum cholesterol as noted previously.

It is an object of the present invention to provide methods and formulations which are useful in long-term treatment of oophorectomized women and women with other forms of ovarian failure.

Summary of the Invention

In accordance with the present invention, there are provided compositions and methods for treating oophorectomized women, wherein an estrogenic composition and an androgenic composition are concurrently administered according to specific protocols as defined herein for long-term, zero-order sustained release. In all protocols an amount of an estrogenic composition effective to prevent symptoms and signs of estrogen deficiency is administered; the symptoms of estrogen deficiency which may develop after oophorectomy include, but not are not limited to, symptoms of the menopause, vasomotor instability, harmful alterations in serum cholesterol or its fractions, and urogenital atrophy. An androgenic composition is concurrently administered in conjunction with the administration of the estrogenic composition. The androgenic composition is administered in an amount effective to increase a patient's effective androgen level to a level not exceeding normal premenopausal levels, and in particular in concert with the estrogenic composition

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Typical dose ranges for estrogenic compositions depend not only upon the choice of composition, but also upon the characteristics of the patient. For an adult human female patient administered estradiol, typical dose ranges are such that the serum level of estradiol is maintained at a level of about 15 to about 50 pg/ml. Most preferably, the serum level of estradiol is about 20 to about 35 pg/ml. These levels are significantly lower than the serum levels achieved in accordance with the ERT regimens in current use which are known to maintain normal bone density. By the term "estradiol equivalents" as used herein is meant the amount of an estrogenic composition that provides a biological effect equivalent to administration of a specified amount of estradiol. As described in some detail hereinafter, the estrogenic composition is administered in a suitable formulation for maintaining a sustained zero-order release, so as to achieve a continuous replacement of a sufficient level of estrogen over the entire period of administration to minimize or eliminate the symptoms and signs of estrogen deficiency.

Concurrent with administration of an estrogenic composition, an androgenic composition is administered in an amount to increase a patient's effective androgen level to a level not exceeding normal premenopausal level, and in particular in concert with the estrogenic composition to maintain BMD. Administration to oophorectomized women of the androgen methyltestosterone has been shown to add significantly to the bone effects of ERT [Watts, N. et al., "Effects of oral esterified estrogens and esterified estrogens plus androgens on bone mineral density in postmenopausal women," North American Menopause Society, Meeting Abstract S-F16 (Montreal, Canada 1991)]. Restoration of a patient's effective normal androgen levels is desirable, as oophorectomy has the effect of reducing effective serum androgen levels, in some cases significantly. For purposes of the present invention, normal androgen levels are on the order of about 20 to about 80 ng/dl for testosterone.

Suitable androgenic hormones for use in accordance with the present invention include, but are not limited to, testosterone, androstenedione, dihydrotestosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyltestosterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone,

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dosage administered. In addition, such microcapsules or microspheres can be successfully sterilized with gamma irradiation.

Microcapsules or microspheres are systems comprising a polymeric wall that encloses a liquid or solid core. The capsule wall usually does not react with the core material; however, it is designed to provide sufficient strength to enable normal handling without rupture while being sufficiently thin to allow a high core to wall volume ratio. The capsule contents remain within the wall until released by diffusion or other means that dissolve, melt, break, rupture or remove the capsule material. Preferably, the capsule wall can be made to degrade and decompose in suitable environments while diffusing the core material through the capsule wall to allow for its slow, prolonged delivery. The mechanism of release in biodegradable microcapsules is a combination of drug diffusion and polymer biodegradation. Therefore, the rate and duration of release are determined by microcapsule size, drug content and quality, and polymer parameters, such as crystallinity, molecular weight and composition. In particular, adjustment in the amount of drug released is generally achieved by modification of capsule wall thickness, capsule diameter, and/or polymer composition.

Detailed information concerning the design and use of microspheres and microcapsules is provided by, e.g., Lewis, D.H., "Controlled release of bioactive agents from lactide/glycolide polymers," in Chasin, M. & Langer, R. (eds.), Biodegradable Polymers as Drug Delivery Systems, pp. 1-41 (1990), the entire disclosure of which is hereby incorporated by reference. Several methods are currently available for preparing microcapsules or microspheres. As discussed in Nuwayser, E.S. et al., "Microencapsulation of contraceptive steroids," in Zatuchni, G.L. et al. (eds.), Long-acting Contraceptive Delivery Systems, pp. 64-76 (1984), the entire disclosure of which is hereby incorporated by reference, most of these methods can be classified under three major categories: coacervation, coagulation and air-suspension coating.

An exemplary material for use in the formulation of suitable microcapsules or microspheres is poly(dl-lactide-co-glycolide) as described in Lewis, D. H. & Tice, T. R., "Polymeric considerations in the design of microencapsulation of contraceptive steroids," in Zatuchni, G. L. et al. (eds.), Long-acting Contraceptive Delivery

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Other suitable materials for preparation of such devices include silicon-based materials, such as polydimethylsiloxanes, which have been employed to prepare capsule-type, matrix-type and microsealed drug delivery systems. For example, a suitable device may be prepared by coating a non-medicated silicone rubber core with a thin layer of silicone rubber (such as MDX-4-4210 Clean Grade Elastomer, available from Dow Corning) which contains micronized crystalline forms of the active agents. An implant of this type (for administration of estradiol) is described in Ferguson, T.H. et al., "Compudose: an implant system for growth promotion and feed efficiency in cattle," J. Controlled Release 8, 45-54 (1988), the entire disclosure of which is hereby incorporated by reference. Improved matrix release devices may be prepared by incorporating water-soluble carriers, such as sodium alginate, or by using additives, such as co-solvents or salts, which enhance the release rate of active agents from the polymer matrix.

In general, contraceptive vaginal rings may be designed as homogeneous mixtures of composition and silastic; as a core vaginal ring surrounded by silastic; as a shell ring with a core of silastic, surrounded by a layer of composition and silastic covered by a tube of silastic; as a band ring of inert silastic with a drug-containing band on the ring; or as a combination of the various designs to permit the specific release characteristics desired. In this regard, useful systems are described in the following: Jackanicz, T. M., "Vaginal ring steroid-releasing systems," pp. 201-12; Diczfalusy, E. & Landgren, B.-M., "Some pharmacokinetic and pharmacodynamic properties of vaginal delivery systems that release small amounts of progestogens at a near zero-order rate," pp. 213-27; and Roy, S. & Mishell, Jr., D.R., "Vaginal ring clinical studies: update," pp. 581-94: all in Zatuchni, G. L. et al. (eds.), Long-acting Contraceptive Delivery Systems (1984), the entire disclosures of which are hereby incorporated by reference.

For transdermal delivery of the active agents, suitable pads or bandages are also well known in the art. Typically, these pads comprise a backing member defining one exterior surface, a surface of pressure-sensitive adhesive defining a second exterior surface, and disposed therebetween a reservoir containing the active agents confined therein. Suitable transdermal delivery systems are disclosed in U.S. Patents 3,731,683 and 3,797,494 to Zaffaroni and U.S. Patent 4,336,243 to

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potential risks inherent in such treatment. Unlike the heretofore known protocols, the present invention calls for administration of amounts of estrogenic and androgenic compositions which in concert achieve the desired effects without the adverse consequences of administering excess amounts of estrogens and/or androgens. Therefore, the androgenic composition is administered in an amount to increase a patient's effective androgen level to a level not exceeding normal premenopausal levels so as to avoid complications associated with excess androgen levels in women, such as hirsutism. Similarly, the estrogenic composition is administered in the lowest amount effective to prevent symptoms and signs of estrogen deficiency, so as to minimize risks associated with higher levels of estrogenic compositions, such as increased risk of breast cancer.

In addition, by maintaining zero-order administration of estrogens and androgens, in accordance with the present invention it is possible to achieve the desired effects with the minimum total doses of both agents. Unlike earlier protocols, in accordance with the present invention at no time will there be excess estrogen or androgen present.

The following example will serve to illustrate the invention without in any way being limiting thereon.

Example

This example describes a delivery system for intramuscular administration over a 4-month duration. The delivery system administers a natural estrogenic steroid (estradiol) and a natural androgenic steroid (testosterone). The serum level of estradiol is maintained at about 40 pg/ml by provision of 5 mg thereof in the form of microspheres prepared from a copolymer of lactide and glycolide; as is well known in the art, this copolymer provides for an effective time-release formulation which is biodegradable. Androgen is provided in a dose of 24 mg of testosterone, also in the form of microspheres prepared from a copolymer of lactide and glycolide, so as to maintain serum levels of testosterone at about 50 ng/dl.

While there have been shown and described the fundamental novel features of the invention, it will be understood that various omissions, substitutions and changes in the form and details of the devices illustrated may be made by those skilled in the art without departing from the spirit of the invention. It is the

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WHAT IS CLAIMED IS:

1. A composition for preventing symptoms and signs of loss of ovarian function in oophorectomized women over a period of time consisting essentially of:

a slow-release formulation of an estrogenic composition which maintains serum level of said estrogenic composition over said period of time at a level effective to prevent symptoms and signs of estrogen deficiency; and

a slow-release formulation of an androgenic hormone which increases serum level of said androgenic hormone over said period of time to a level not exceeding a normal premenopausal level for a patient.

2. A composition according to claim 1, wherein said estrogenic composition is selected from the group consisting of estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylstilbestrol, piperazine estrone sulfate, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, quinestrol, estropipate, pinestrol, estrone potassium sulfate, equilelinin, equilelinin sulfate, estetrol and mixtures of two or more thereof.

3. A composition according to claim 1, wherein said androgenic hormone is selected from the group consisting of testosterone, androstenedione, dihydrotestosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyltestosterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymethalone, stanozolol and testolactone.

4. A composition according to claim 1, wherein said period of time is about 3 days to about five years.

5. A composition according to claim 4, wherein said period of time is about three months to about four months.

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13. A method according to claim 12, wherein said period of time is about three months to about four months.

14. A method according to claim 11, wherein said estrogenic composition is selected from the group consisting of estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylstilbestrol, piperazine estrone sulfate, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, quinestrol, estropipate, pinestrol, estrone potassium sulfate, equilelinin, equilelinin sulfate, estetrol and mixtures of two or more thereof.

15. A method according to claim 11, wherein said androgenic hormone is selected from the group consisting of testosterone, androstenedione, dihydrotestosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyltestosterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymethalone, stanozolol and testolactone.

16. A method according to claim 11, wherein said serum level of said androgenic composition is equivalent to serum testosterone levels in the range of about 20 to about 80 ng/dl.

17. A method according to claim 11, wherein said serum level of said estrogenic composition is equivalent to serum estradiol levels in the range of about 20 to about 35 pg/ml.

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